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EXAMINER	
MUMMERT, STEPHANIE KANE	

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1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/052,926	Applicant(s) SAMPSON, JEFFREY R.
	Examiner Stephanie K. Mummert, Ph.D.	Art Unit 1637

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35,67-101 and 144-149* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-35,67-101 and 144-149* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

The Examiner of record has changed. Please address all future correspondence to Examiner Mummert, whose contact information is included at the conclusion of this communication.

Applicant's amendment filed on April 30, 2007 is acknowledged and has been entered. Claims 1-35, 67-101 and 144-149 are pending.

Applicant's arguments with respect to claims 1-35, 67-101 and 144-149 have been considered but are moot in view of the new ground(s) of rejection.

All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-35, 67-101 and 144-149 are pending and will be examined.

This action is NON-FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-35, 67-101 and 144-149 are rejected under 35 U.S.C. 112, first paragraph, because the specification is not enabling for determining the sequence of nucleic acids by passing these nucleic acids as the molecule passes through a channel or nanochannel. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

<u>The nature of the invention</u>

Claims 1-35, 67-101 and 144-149 are directed to a method for identifying individual units of a nucleic acid, comprising moving a nucleic acid linearly through a channel to determine the sequence of the nucleic acid molecule. The invention is in an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims encompass a method directed to the identification of the specific units of a polymer, comprising taking measurements as a nucleic acid passes through a microchannel, passing from one pool to another and determining the sequence of the nucleic acid molecule.

Quantity of Experimentation

The quantity of experimentation in this area is large. Regarding the formation of the nanochannel pores and their application to the practice of determining the sequence of individual units of a polymer through linear analysis, Applicant has given no indication that such an apparatus or device, comprising nanochannels or a nanoplate has been reduced to practice. A post-filing reference, Chan (Chan, Eugene, Mutation Research, 2005, 573, p. 13-40) notes that "a single-base resolution strategy has yet to be articulated with solid-state nanopores" (p. 30 col. 2 to p. 31 col. 1). The Court in In re Ghiron, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. While Applicant describes the essential features of such an apparatus in the specification, the fabrication of such a device is not described in the specification in such detail as to obviate undue experimentation by one of ordinary skill in the art. The following paragraph discusses some features of the apparatus required to practice the claimed methods that are unpredictable and would therefore require undue experimentation for reduction to practice.

<u>The unpredictability of the art and the state of the prior art</u>

The current state of the art indicates that a great deal of further experimentation and inventiveness would be required to implement the methods claimed by Applicant.

Regarding the practice of the method of sequencing using a nanochannel, Chan (EY, 2005, 573, p. 13-40) notes that "work in the field of nanopore sequencing has focused on the development of solid-state nanopores that may bypass some of the inherent limitations of protein pores. For instance the use of solid state nanopores allows the use of denaturing conditions suitable for single-stranded DNA." Chan also notes "these nanopores have been used effectively to analyze DNA conformations, and mediate DNA transport with single-base pair mismatch selectivity". However, Chan also notes that "resolution remains an issue for these methods; it is challenging to fabricate a robust nanopore that is less that 3.4 Å in length, the interbase distance. A single-base pair resolution strategy has yet to be articulated with solid-state nanopores" (p. 30, col. 2).

Currently, the state of the art even after the filing of the instant application appears to be at the point where single molecules can be transported and detected at the single molecule level. Details such as length, strandedness, conformation, heterogeneity and some sequence information can be established (p. 580-585 of Rhee), however obtaining sequence information at the individual linked unit level, particularly along the entire length of a polymer such as nucleic acids or polypeptides appears highly unpredictable. Rhee et al. (Trends in Biotechnology, 2006, vol. 24, no. 12, p. 580-586) states "Protein or synthetic nanopores have been used to detect DNA or RNA molecules. Although none of the technologies to date has shown single-base resolution

for de novo sequencing, there have been several reports of α-hemolysin protein nanonpores being used for basic DNA analysis" (Abstract).

Therefore, the current state of the art demonstrates that the inclusion of a light emissive compound on each individual unit of a polymer, nucleic acid particularly, would be subject to a high degree of unpredictability. Furthermore, regarding the practice of the invention wherein the station is embedded within a nanochannel, the current state of the art suggests a high degree of unpredictability and potentially a lack of function as applies to the method of claim 1.

Working Examples

The specification has no working examples.

Guidance in the Specification.

The specification, discloses multiple embodiments for the practice of the claimed methods, including the method as disclosed at claims 1-35, 67-101 and 144-149.

The specification provides general guidance regarding the practice of the invention. The specification teaches the components of the method, including the format of the polymer template for sequencing (including the unstructured nucleic acid embodiment) (p. 7-10 of PgPub). The specific nanopores useful for sequencing one or multiple polymers simultaneously are described as including a variety of passages including ion channels or ion permeable pores (paragraph 121-124 of PgPub). The specific nucleic acid monomers are identified in a variety of ways. For example, the nucleotide sequence can be established through ion conductance, "The characteristics of the nucleic acid can be identified by the amplitude or duration of individual

conductance changes across the passage. Such changes can identify the monomers in sequence, as each monomer will have a characteristic conductance change signature. For instance, the volume, shape, or charges on each monomer will affect conductance in a characteristic way" (paragraph 126 of PgPub). In another embodiment, the nucleotide sequence is established by measuring deflection as nucleotides are pulled through the interface between the pools, "The measurement of the interactions can be by a detector that measures the deflection of the interface (caused by each nucleotide passing through the interface) using reflected or refracted light, or a sensitive gauge capable of measuring intermolecular forces" (paragraph 130 of PgPub).

The specification does not provide specific examples of the application of these methods to specific nucleic acids in the format of a working example. The teachings in the specification appear to be prophetic teachings.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the linear sequence analysis of the method of the claims, in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define unpredictable variables, the lack of guidance provided in the specification, the presence of no working examples and the negative teachings in the prior art balanced only against the high skill level in the art, it is concluded that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Claim Interpretation

While the term 'modified nucleotide' is provided a definition in the specification, the definition does not provide an explicit definition of the term. Instead, the term is defined in general terms such as "Modified bases (excluding A, T, G, C, and U) include for example, bases having a structure derived from purine or pyrimidine (i.e. base analogs). For example without limitation, a modified adenine may have a structure comprising a purine with a nitrogen atom covalently bonded to C6 of the purine ring as numbered by conventional nomenclature known in the art" (paragraph 17 of PgPub). The specification also teaches that the modified nucleotide has "a reduced ability to form basepairs with complementary modified or unmodified nucleic acids" (paragraph 10 of PgPub). Therefore, the term is being interpreted as reading on art directed to the inclusion of any kind of nucleotide that reduces hydrogen bonding or basepairing between 'natural' and modified oligonucleotide sequences.

The term 'at least one repeat of a nucleic acid' is not provided with an explicit definition in the specification. Instead, the term is defined in general terms such as "the present invention generates nucleic acid polymers for nanopore sequencing having multiple tandem repeats" (paragraph 8 of PgPub). Therefore, as the term requires at least one repeat and not tandem repeats, and without an explicit definition, the term is being interpreted as reading on art directed to any repeated nucleotide sequences in the nucleic acid.

Claim Rejections - 35 USC § 103

2. Claims 1-5, 8-30, 32-33, 67-71, 75-76 and 78-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Church et al. (US Patent 5,795,782; August 1998) in view of Morgan et al. (Biochemistry 1980, vol. 19, no. 26, p. 5960-5966). Church teaches a method of sequencing a nucleic acid by measuring changes across an interface between two pools of media (Abstract).

With regard to claim 1 and 67, Church teaches a method of sequencing a nucleic acid molecule comprising steps of:

providing two separate, adjacent pools of a medium and an interface between the two pools, the interface having a channel so dimensioned as to allow sequential nucleotide-by-nucleotide passage from one pool to the other pool of only one nucleic acid molecule at a time (Figure 1, where the method is depicted schematically; col. 1, line 35, col. 2, line 8, where two adjacent pools of medium are provided with an interface which is capable of interacting with individual monomer residues of a single polymer); producing a nucleic acid molecule with at least one repeat of a nucleotide sequence to be determined (col. 11, lines 38-41, where nucleic acids with repeating identical bases are resolved, where 'punctuation' in the conductance is registered through a distinct/higher level of conductance between bases); placing the nucleic acid molecule in one of the two pools; and taking measurements as each of the nucleotides of the nucleic acid molecule passes through the channel so as to determine the sequence of the nucleic acid molecule (col. 1, line 35 to col. 2, line 8, where a single polymer is present in one of the two pools and interface dependent measurements are taken leading to characterization of polymers in the mixture and the method can be used to determine their sequence).

With regard to claim 2 and 68, Church teaches an embodiment of claim 1 and 67, wherein the nucleic acid is single- stranded (col. 7, lines 31-34; col. 10, lines 18-24, where the nucleic acid comprises single or double-stranded DNA).

With regard to claim 3 and 69, Church teaches an embodiment of claim 2 and 68, wherein the nucleic acid is single-stranded DNA (col. 7, lines 31-34; col. 10, lines 18-24, where the nucleic acid comprises single or double-stranded DNA).

With regard to claim 4 and 70, Church teaches an embodiment of claim 2 and 68, wherein the nucleic acid is single-stranded RNA (col. 7, lines 31-34; col. 10, lines 18-24, where the nucleic acid comprises single or double-stranded DNA; col. 7, lines 55-60, where the polymer can comprise RNA).

With regard to claim 8 and 78, Church teaches an embodiment of claim 1 and 67, wherein the medium is electrically conductive (col. 2, lines 35-37, where the pools include electrically conductive medium, either the same or different composition; col. 2, lines 59-64, where the electrically conductive medium can be any medium, including an aqueous solution).

With regard to claim 9, 20, 28, 79, 90, 98, Church teaches an embodiment of claim 8, 19, 27, 78, 89, 97, wherein the medium is an aqueous solution (col. 2, lines 9-13, where the pools are liquids, usually aqueous solutions; col. 2, lines 59-64, where the conducting medium is any medium and preferably an aqueous solution).

With regard to claim 10, 14, 21, 23, 80, 84, 91, 93, Church teaches an embodiment of claim 8, 9, 20, 22, 78, 79, 90, 92, further comprising applying a voltage across the interface (col. 2, line 64 to col. 3, line 3, where voltage is applied across the barrier between the pools; col. 4, lines 57-67, where the passage is preferably voltage sensitive or voltage-gated).

With regard to claim 11, 15, 22, 24, 29, 30, 81, 85, 92, 94, 99, Church teaches an embodiment of claim 10, 14, 21, 23, 27, 28, 81, 84, 91, 93, 98, wherein ionic flow between the two pools is measured (col. 2, lines 35-47, where the conductive pools are separated by an impermeable barrier with an ion-permeable passage, an electrical potential between the two pools is established and ionic current is allowed to flow across the passage).

With regard to claim 12, 16, 25, 82, 86, 95, 100, Church teaches an embodiment of claim 11, 15, 24, 81, 85, 94, 97, wherein the duration of ionic flow blockage is measured (col. 4, lines 31-35, the characteristics of the polymer can be identified by amplitude and duration of individual conductance changes across the passage).

With regard to claim 13, 17, 26, 83, 87, 96, Church teaches an embodiment of claim 11, 15, 25, 81, 84, 94, wherein the amplitude of ionic flow blockage is measured (col. 4, lines 31-35, the characteristics of the polymer can be identified by amplitude and duration of individual conductance changes across the passage).

With regard to claim 18 and 88, Church teaches an embodiment of claim 1 and 67, wherein the nucleic acid polymer interacts with an inner surface of the channel (col. 6, lines 59-65, where the polymer passage through the interface results in monomer interactions with the interface that are sufficient to identify the monomers or the characteristics of the polymer; col. 20, lines 24-29, where "short duration blockades represent polymers that interact with the channel (e.g., loops of polymer that come to lie on the channel aperture)").

With regard to claim 19 and 89, Church teaches an embodiment of claim 18 and 88, wherein the medium is electrically conductive (col. 2, lines 35-37, where the pools include

electrically conductive medium, either the same or different composition; col. 2, lines 59-64, where the electrically conductive medium can be any medium, including an aqueous solution).

With regard to claim 27 and 97, Church teaches an embodiment of claim 1 and 67, further comprising providing a polymerase or exonuclease in one of the two pools, wherein the polymerase or exonuclease draws the nucleic acid polymer through the channel (col. 7, lines 27-31, where a polymerase is fused with the pore to pull the nucleic acid through the channel; col. 12, lines 65-67).

Regarding claim 1 and 67, Church does not teach the steps wherein the nucleic acid molecule contains modified nucleotides that reduce secondary structure in the nucleic acid molecule.

With regard to claims 1 and 67, Morgan teaches a method comprising producing a nucleic acid molecule wherein the nucleic acid molecule contains modified nucleotides that reduce secondary structure in the nucleic acid molecule (Abstract, where substitution of inosine for guanosine resulted in absence of G-C base pairs and loss of ordered secondary structure; p. 5962, col. 2, where I-substituted transcripts migrated more slowly than transcripts with normal G residues and "probably resulted from loss of intermolecular base pairing").

With regard to claim 5 and 71, Morgan teaches an embodiment of claim 1 and 67, wherein the nucleic acid is an unstructured nucleic acid (Abstract, where substitution of inosine for guanosine resulted in absence of G-C base pairs and loss of ordered secondary structure; p. 5962, col. 2, where I-substituted transcripts migrated more slowly than transcripts with normal G residues and "probably resulted from loss of intermolecular base pairing").

With regard to claim 32 and 75, Morgan teaches an embodiment of claim 1 and 67, wherein the nucleic acid molecule contains modified guanosine and modified cytosine which are not able to form base pairs, wherein the modified guanosine is capable of forming a base pair with unmodified cytosine, and wherein the modified cytosine is capable of forming a base pair with unmodified guanosine (p. 5965, col. 1, where the lower stability of I-C as compared to G-C base pairs are discussed. In I-C base pairs there are 2 hydrogen bonds, while in G-C base pairs there are 3 hydrogen bonds present, however base pairing does occur, it is less stable).

With regard to claim 33 and 76, Morgan teaches an embodiment of claim 1 and 67, wherein the nucleic acid molecule contains 2-aminoadenosine, 2-thiothymidine, inosine, and pyrrolopyrimidine (Abstract, where substitution of inosine for guanosine resulted in absence of G-C base pairs and loss of ordered secondary structure; p. 5962, col. 2, where I-substituted transcripts migrated more slowly than transcripts with normal G residues and "probably resulted from loss of intermolecular base pairing").

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied and incorporated the modified nucleotides of Morgan to the practice of sequencing of nucleic acids as taught by Church to arrive at the claimed invention with a reasonable expectation for success. Church teaches the inclusion of a variety of modified nucleotides, but does not teach the specific inclusion of modified analogues to affect secondary structure of templates for sequencing. Morgan teaches a method that incorporates inosine residues in place of guanosine residues in transcripts and examines the effect on secondary structure, binding and elongation. Morgan finds that "the apparent molecular weights of the I-substituted products were altered as a consequence of the absence of G-C basepairs and

accompanying loss of ordered structure" (Abstract).. Therefore, the method of sequencing as taught by Church is known as stated above. Church does not teach the inclusion of modified nucleotides to affect secondary structure. Morgan teaches the substitution of guanosine with inosine and results in a change in secondary structure of the nucleic acid. Therefore, considering the teachings of Morgan and Church, it would have been prima facie obvious to one of ordinary skill in the art to modify the secondary structure of template nucleic acid molecules prior to passing these molecules through a pore for establishing sequence identity using the known technique taught by Morgan to yield a predictable result.

3. Claims 6-7, 72-73 and 148-149 are rejected under 35 U.S.C. 103(a) as being unpatentable over Church et al. (US Patent 5,795,782; August 1998) in view of Morgan et al. (Biochemistry 1980, vol. 19, no. 26, p. 5960-5966) as applied to claims 1-5, 8-30, 32-33, 67-71, 75-76 and 78-100 above, and further in view of Lizardi et al. (US Patent, 6,632,609; October 2003). Church teaches a method of sequencing a nucleic acid by measuring changes across an interface between two pools of media (Abstract).

Church in view of Morgan teach all of the limitations of claims 1-5, 8-30, 32-33, 67-71, 75-76 and 78-100. Neither Church or Morgan teach that the nucleic acid is produced using a circular template. Lizardi teaches the synthesis and amplification of circular nucleic acid templates (Abstract).

With regard to claim 6 and 73, Lizardi teaches an embodiment of claim 1, wherein the nucleic acid is enzymatically produced using circular template that is single-stranded or double-

stranded (Figures 1-4, where the open circle probe is single stranded and is ligated to form a circular template on the specific target nucleic acid and is therefore enzymatically produced).

With regard to claim 7 and 72, Lizardi teaches an embodiment of claim 6, wherein the circular template is single stranded (Figures 1-4, where the open circle probe is single stranded and is ligated to form a circular template on the specific target nucleic acid and is therefore enzymatically produced).

With regard to claim 148 and 149, Lizardi teaches an embodiment of claim 1 and 67, wherein said producing comprises contacting a circular template with a primer, a polymerase, nucleotides and modified nucleotides under rolling circle amplification conditions sufficient to produce said nucleic acid (col. 3, lines 1-32, where the amplification comprises these components; see also Figures 3 and 4, for example).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of circular template production of Lizardi to the method of sequencing taught by Church to arrive at the claimed invention with a reasonable expectation for success. Church in view of Morgan teach sequence analysis of nucleic acids comprising modified nucleotides. However, neither Church or Morgan teach that the template comprises a circular template. Lizardi teaches "The DNA ligation operation circularizes a specially designed nucleic acid probe molecule. This step is dependent on hybridization of the probe to a target sequence and forms circular probe molecules in proportion to the amount of target sequence present in a sample" (col. 3, lines 10-14). Therefore, considering the circular templates taught by Lizardi, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the circular templates taught by

Lizardi and this incorporation would have provided a predictable outcome with a reasonable expectation for success.

4. Claims 31, 34, 74, 77 and 144-147 are rejected under 35 U.S.C. 103(a) as being unpatentable over Church et al. (US Patent 5,795,782; August 1998) in view of Morgan et al. (Biochemistry 1980, vol. 19, no. 26, p. 5960-5966) as applied to claims 1-5, 8-30, 32-33, 67-71, 75-76 and 78-100 above, and further in view of Kutyavin et al. (US Patent 5,912,340; June 1999). Church teaches a method of sequencing a nucleic acid by measuring changes across an interface between two pools of media (Abstract).

Church in view of Morgan teach all of the limitations of claims 1-5, 8-30, 32-33, 67-71, 75-76 and 78-100. Neither Church or Morgan teach the inclusion of a modified adenosine or thymine. Kutyavin teaches modified bases that form less stable hydrogen bonds, which decreases melting temperature (Abstract).

With regard to claim 31 and 74, Kutyavin teaches an embodiment of claim 1 and 67, wherein the nucleic acid molecule contains modified adenosine and modified thymine which are not able to form base pairs, wherein the modified adenosine is capable of forming a base pair with unmodified thymine, and wherein the modified thymine is capable of forming a base pair with unmodified adenosine (col. 5, lines 37-61, where the general structure of the preferred A analog, A' is described, wherein a preferred embodiment comprises 2-aminoadenine; col. 6, line 56 to col. 7, line 10, where the general structure of the preferred T is described and wherein a preferred embodiment comprises 2-thiothymine).

With regard to claim 34 and 77, Kutyavin teaches an embodiment of claim 1 and 67, wherein the nucleic acid molecule contains 2-aminoadenosine, and 2-thiothymidine (col. 5, lines 37-61, where the general structure of the preferred A analog, A' is described, wherein a preferred embodiment comprises 2-aminoadenine; col. 6, line 56 to col. 7, line 10, where the general structure of the preferred T is described and wherein a preferred embodiment comprises 2-thiothymine; Abstract, where it is noted that "the ODNs include modified bases of such nature that the modified base forms a stable hydrogen bonded base with the natural partner base, but does not form a stable hydrogen bonded base pair with the modified primer" and notes "due to the lack of stable hydrogen bonding with each other, the matched pair of oligonucleotides have a melting temperature" which is 40oC or less).

With regard to claim 144 and 146, Kutyavin teaches an embodiment of claim 1 and 67, wherein the nucleic acid molecule contains a modified thymine (col. 5, lines 37-61, where the general structure of the preferred A analog, A' is described, wherein a preferred embodiment comprises 2-aminoadenine; col. 6, line 56 to col. 7, line 10, where the general structure of the preferred T is described and wherein a preferred embodiment comprises 2-thiothymine).

With regard to claim 145 and 147, Kutyavin teaches an embodiment of claim 1 and 67, wherein the nucleic acid molecule contains 2-thiothymidine (col. 5, lines 37-61, where the general structure of the preferred A analog, A' is described, wherein a preferred embodiment comprises 2-aminoadenine; col. 6, line 56 to col. 7, line 10, where the general structure of the preferred T is described and wherein a preferred embodiment comprises 2-thiothymine).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the teachings of modified bases by Church in view of

Morgan to replace adenine and thymine in the nucleic acids of the invention to include the 2-aminoadenine and 2-thiothymine of Kutyavin to arrive at the claimed invention with a reasonable expectation for success. As taught by Kutyavin, "the ODNs include modified bases of such nature that the modified base forms a stable hydrogen bonded base with the natural partner base, but does not form a stable hydrogen bonded base pair with the modified primer" and notes "due to the lack of stable hydrogen bonding with each other, the matched pair of oligonucleotides have a melting temperature" which is 40oC or less (Abstract). While neither Church or Morgan teaches the inclusion of analogues for A and T, Kutyavin teaches analogues for each nucleotide monomer and the reduction in hydrogen bonding stability. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have incorporated these additional analogues and reduction in binding strength associated with both analogues to arrive at the claimed invention with a reasonable expectation for success.

5. Claims 35 and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Church et al. (US Patent 5,795,782; August 1998) in view of Morgan et al. (Biochemistry 1980, vol. 19, no. 26, p. 5960-5966) as applied to claims 1-5, 8-30, 32-33, 67-71, 75-76 and 78-100 above, and further in view of Thorp et al. (US Patent 5,871,918; February 1999). Church teaches a method of sequencing a nucleic acid by measuring changes across an interface between two pools of media (Abstract).

Church in view of Morgan teach all of the limitations of claims 1-5, 8-30, 32-33, 67-71, 75-76 and 78-100. Neither Church or Morgan teach the analysis of nucleic acids by electron tunneling.

With regard to claim 35 and 101, Thorp teaches an embodiment of claim 1 and 67, further comprising analyzing the nucleic acid molecules by electron tunneling (col. 9, line 18 to col. 10, lines 42, where in specific embodiments, the nucleic acid molecules are analyzed by electron tunneling).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the method of sequencing of Church to include the technique of electron tunneling detection of nucleic acid molecules as taught by Thorp to arrive at the claimed invention with a reasonable expectation for success. Church in view of Morgan teach the sequencing of nucleic acids, however neither teach the application of electron tunneling to the analysis of nucleic acid molecules. Thorp teaches the application of electron tunneling and notes that "correlation between the tunneling distance and the specific base paired with the preselected base is therefore established" (col. 10, lines 9-11). Therefore, as Thorp teaches that electron tunneling may be used to analyze nucleic acids, one of ordinary skill in the art at the time the invention was made would have been motivated to have extended the method of sequencing of Church to include the technique of electron tunneling detection of nucleic acid molecules as taught by Thorp to arrive at the claimed invention with a reasonable expectation for success.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie K. Mummert, Ph.D. whose telephone number is 571-272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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